Antiphospholipid syndrome and challenges with direct oral anticoagulants

Abstract

Direct oral anticoagulants have become the mainstay of the management of venous thromboembolism and atrial fibrillation, and long-term anticoagulation is indicated for those at high risk of further thrombotic events. This includes patients diagnosed with antiphospholipid syndrome, for whom the 'triple positive' laboratory combination of lupus anticoagulant, β2-glycoprotein-1 and anti-cardiolipin antibodies signify those at greatest risk. Data from meta-analysis and randomised control trials have raised the concern that direct oral anticoagulants may be less effective than vitamin K antagonists for the prevention of thrombosis in patients with thrombotic antiphospholipid syndrome, particularly those with the triple positive profile. This article reviews the diagnosis of thrombotic antiphospholipid syndrome, strategies for testing without interruption of anticoagulation, evidence concerning the safety of direct oral anticoagulants in this setting, and the implications for current investigation and management of unprovoked venous thromboembolism.

Key words: Antiphospholipid syndrome; Direct oral anticoagulant; Lupus anticoagulant

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Introduction

Thrombotic antiphospholipid syndrome is defined by the association of arterial, venous or microvascular thrombosis and laboratory features of persistent antiphospholipid antibodies. Obstetric antiphospholipid syndrome shares these laboratory features but clinically manifests through recurrent pregnancy loss and fetal morbidity.

Thrombotic antiphospholipid syndrome most commonly presents with venous thromboembolism, but also may present with arterial thrombosis, particularly stroke. In the Euro-Phospholipid cohort of 1000 patients with antiphospholipid syndrome, 53% had venous thromboembolism and 19.8% had stroke (Cervera et al, 2009). Management of venous thrombosis in antiphospholipid syndrome has traditionally been with vitamin K antagonists at a target international normalised ratio of 2.5, while management of arterial thrombosis has been with antiplatelet agents and/or vitamin K antagonists at a target international normalised ratio of either 2.5 or 3.5 (Tektonidou et al, 2019). Microvascular thrombosis may give rise to a variety of clinical manifestations, including livedo reticularis or infarction affecting any of the skin, brain, myocardium, kidney, lung or gut. A fulminant presentation of catastrophic antiphospholipid syndrome affects a small number of patients (0.8% in the Euro-Phospholipid cohort).

Venous thromboembolism is common, with an estimated incidence of 131.5 per 100 000 person years in the UK (Martinez et al, 2014). Antiphospholipid antibodies are reported to be detectable in around 10% of patients presenting with a deep venous thrombosis (Andreoli et al, 2013).

Venous thromboembolism is usually managed with oral anticoagulation of either fixed duration, where there is low risk of recurrence (such as venous thromboembolism with a strong provoking factor) or extended duration, where there is a high risk of recurrence that outweighs the associated bleeding risk (such as most unprovoked venous thromboembolism). Persistent antiphospholipid antibodies in a patient with thrombosis are diagnostic of thrombotic antiphospholipid syndrome and an indication for extended anticoagulation.

The direct oral anticoagulants have revolutionised anticoagulation practice for both atrial fibrillation and venous thromboembolism, and have now replaced vitamin K antagonists as the most commonly prescribed oral anticoagulants (OpenPrescribing.net et al, 2020).

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Table 1. Diagnosing thrombotic antiphospholipid syndrome: the Sydney–Sapporo criteria	
Clinical criteria	Vascular thrombosis: one or more clinical episodes of arterial, venous or small vessel thrombosis
Laboratory criteria	1. Lupus anticoagulant present in plasma, on two or more occasions at least 12 weeks apart
	2. Anticardiolipin antibody of immunoglobulin G or M isotype present in medium or high titre (ie >40G or M phosopholipid units, or > the 99th centile), on two or more occasions, at least 12 weeks apart
	3. Anti-β2–glycoprotein 1 antibody of IgG isotype (in titre >the 99th centile), present on two or more occasions at least 12 weeks apart
Antiphospholipid antibody syndrome is present if at least one of the clinical criteria and one of the laboratory criteria are met	

Adapted from Miyakis et al (2006) with permission

Direct oral anticoagulants currently licenced in the UK include the factor Xa inhibitors apixaban, rivaroxaban and edoxaban, and the direct thrombin inhibitor dabigatran. Their advantages over the vitamin K antagonists include fixed dosing, greatly reduced need for monitoring blood tests and equivalent or improved safety profiles in both randomised trial and real world data (Agnelli et al, 2013; Vinogradova et al, 2018). However, direct oral anticoagulants are not suitable for all patients, particularly those with renal impairment, metallic heart valves (Eikelboom et al, 2013), or very low body weight.

Safety concerns, including a warning from the Medicines and Healthcare products Regulatory Agency (2019), have put a spotlight on the role of direct oral anticoagulants in patients with thrombotic antiphospholipid syndrome. Re-evaluation of current pathways of investigation of unprovoked venous thromboembolism and the management of patients with thrombotic antiphospholipid syndrome is therefore required. This review explores the evidence regarding use of direct oral anticoagulants in patients with antiphospholipid syndrome and considers the implications for UK practice.

Antiphospholipid syndrome: definition and diagnosis

Diagnostic criteria for antiphospholipid syndrome

Thrombotic antiphospholipid syndrome is defined according to the 2006 international consensus statement (Miyakis et al, 2006) (Table 1). The diagnosis requires the combination of both clinical features (of arterial, venous or microvascular thrombosis) and laboratory features (of persistent antiphospholipid antibodies).

There are three principal tests for antiphospholipid antibodies:

1. Lupus anticoagulant
2. IgM and IgG anti-cardiolipin antibodies
3. IgM and IgG anti-β2-glycoprotein 1 antibodies (Keeling et al, 2012).

Cardiolipin is a mitochondrial membrane component that complexes with β2-glycoprotein 1. Antiphospholipid antibodies are directed against either the complex as a whole in the older anti-cardiolipin assay, or against β2-glycoprotein specifically. Antiphospholipid antibodies can interact with the phospholipid involved in coagulation tests, such as the activated partial thromboplastin time, and result in their prolongation, which corrects on addition of phospholipid. This is known as a lupus anticoagulant, but is neither a test for lupus nor an anticoagulant.

Patients may be positive for one or more of these tests. To diagnose antiphospholipid syndrome, antiphospholipid antibodies must be demonstrated on two occasions more than 12 weeks apart (Miyakis et al, 2006). Patients for whom all three tests are positive are termed ‘triple positive antiphospholipid syndrome’ and these patients have the greatest risk of recurrent thrombosis. A number of additional clinical manifestations such as thrombocytopenia and livedo reticularis are recognised but are not included in the diagnostic criteria (Meroni et al, 2014).

Obstetric antiphospholipid syndrome is the term used when antiphospholipid syndrome manifests clinically through miscarriage or late pregnancy complications, which include pregnancy loss, intrauterine growth restriction, pre-eclampsia and abruption. Both thrombotic and obstetric antiphospholipid syndrome can occur in the same woman.

Antiphospholipid syndrome may occur in isolation or alongside other autoimmune conditions, for example it is estimated to occur in 15% of patients with systemic lupus erythematosus (Ruiz-Irastorza et al, 2011) in whom active inflammation may further promote thrombotic risk (Sanchez-Redondo et al, 2019). The most severe manifestation of thrombosis is catastrophic antiphospholipid syndrome, whereby patients experience life-threatening thrombosis in three or more organs within a week (Asherson et al, 2003).

Prevalence of antiphospholipid antibodies in the general population

Antiphospholipid antibodies are estimated to be detectable in 1–5% of healthy people with no history of thrombosis and alone do not signify a diagnosis of antiphospholipid syndrome (Chaturvedi and McCrae, 2017). Overall, this group has a comparatively low risk of thrombosis of around 1% per year. The risk of thrombosis is highest in those with all three antiphospholipid antibodies with a risk of first thrombosis closer to 5% per year (Pengo et al, 2011). However, there is currently no recommendation to anticoagulate such patients in the absence of a history of thrombosis.

Patients with positive antiphospholipid antibodies have an estimated 40% higher risk of recurrence after a first venous thromboembolism than those without antiphospholipid antibodies (Garcia et al, 2013). In patients with antiphospholipid syndrome treated with vitamin K antagonists, with a target international normalised ratio of 2–3, there is a significant reported recurrence rate of 5.5% over 3.5 years, despite therapeutic international normalised ratios (Crowther et al, 2003; Finazzi et al, 2005).

Indications for antiphospholipid antibody testing

Both the National Institute for Health and Care Excellence (2020) and the British Society for Haematology (Keeling et al, 2012) recommend testing for antiphospholipid antibodies in patients who have had an unprovoked proximal venous thromboembolism and for whom cessation of anticoagulation is being considered, typically at the end of the initial 3-month treatment period. It is important to recognise that extended anticoagulation is indicated for most patients with an unprovoked venous thromboembolism, regardless of antiphospholipid syndrome status, in view of the relatively high risk of recurrence (Khan et al, 2019). In the era of vitamin K antagonists there was therefore only a select group of patients with unprovoked venous thromboembolism in whom antiphospholipid syndrome testing was useful clinically: specifically in deciding whether to discontinue a patient from anticoagulation who appeared otherwise low risk for recurrent thrombosis. In the context of ischaemic stroke, both the British Society for Haematology and Royal College of Physicians national guidelines recommend antiphospholipid antibody testing in patients under 50 years of age (Keeling et al, 2012; Royal College of Physicians, 2016).

Challenges and recommendations for antiphospholipid antibody testing on direct oral anticoagulants

Testing for β2-glycoprotein-1 and anti-cardiolipin antibodies is by enzyme-linked immunosorbent assay (ELISA) or chemiluminescent techniques, which are not affected by direct oral anticoagulants (Seheult et al, 2017). They can be referred to as ‘solid phase antibodies’ and initial testing may be undertaken when a venous thromboembolism is diagnosed (Arachchillage et al, 2020).

Lupus anticoagulant testing relies on coagulation times and is more complex, with the potential for interference by direct oral anticoagulants. The most common method is the dilute Russell Viper venom time test, with a second test such as the activated partial thromboplastin time to improve sensitivity. Both the dilute Russell Viper venom time test

and activated partial thromboplastin time rely on demonstrating a prolonged clotting time (referred to as the 'screen') that is at least partially corrected by adding extra phospholipid (referred to as the 'confirm') (Miyakis et al, 2006). Lupus anticoagulant testing should generally be avoided on samples at the time of presentation with venous thromboembolism because transient false positive results that are not clinically significant are relatively frequent in this group (Arachchillage et al, 2020).

All the commonly prescribed direct oral anticoagulants may prolong coagulation times with variation depending on the precise reagents used. This may give rise to false-positive results in lupus anticoagulant testing (Seheult et al, 2017; Favaloro, 2019). However, the extent of these effects may vary between the screen and confirm elements of the test, which are then often expressed as a ratio and results in the potential for paradoxical false negatives, a phenomenon that has been reported with apixaban (Favaloro, 2019).

There are potential solutions to these concerns, such as an alternative lupus anticoagulant assay based on Textarin or Taipan venom which are not thought to be influenced by direct oral anticoagulants (Arachchillage et al, 2015). Furthermore, it is feasible to adsorb direct oral anticoagulants from laboratory plasma samples with a commercial product (DOAC-Stop), allowing lupus anticoagulant testing (Zabczyk et al, 2019). However, both of these techniques require specialist haemostasis expertise, are not available in many laboratories and do not have external quality assessment schemes.

The British Society for Haematology has recently issued updated guidance advising that conventional lupus anticoagulant testing should not be performed in patients taking direct oral anticoagulants where there is a detectable drug level (Arachchillage et al, 2020). In practice, conventional testing for lupus anticoagulant will therefore require a wash-out period of several days after stopping the direct oral anticoagulant, depending on the patient's renal function.

For patients considered at particularly high risk of recurrence during any interruption to anticoagulation, such as those with a previously demonstrated solid phase antibody, switching temporarily to low molecular weight heparin may permit testing. While low molecular weight heparin also has the potential to influence lupus anticoagulant assays depending on the reagents used, the effect is much less significant than that observed with direct oral anticoagulants, especially if samples are taken immediately before the next dose of low molecular weight heparin is due. With regard to vitamin K antagonists, some laboratories have established protocols for testing patients but must be informed of the anticoagulant to account for it (Keeling et al, 2012). It is therefore crucial to liaise with the testing laboratory before considering sending lupus anticoagulant samples for patients who are taking anticoagulants.

Direct oral anticoagulants in antiphospholipid syndrome: current evidence

There has been accumulating clinical evidence giving rise to concern about the use of direct oral anticoagulants in patients with established antiphospholipid syndrome.

Case series

A meta-analysis (Dufrost et al, 2018) reviewed the outcomes of 447 published patients treated with direct oral anticoagulants (319 from case reports and series, 57 in the RAPS study and 71 in the original direct oral anticoagulant licencing studies). The rate of recurrent thrombosis was 16% at a median of 12.5 months, with a roughly even spread of venous and arterial events. Of note, in the triple positive population the rate of thrombosis was significantly higher, at 33%. These data have obvious limitations of potential publication bias but raise concerns that direct oral anticoagulants may not be suitable in patients with antiphospholipid syndrome, particularly in the highest risk groups.

Randomised controlled trials

Three published prospective randomised controlled trials have examined the role of direct oral anticoagulants in antiphospholipid syndrome directly and a fourth (ASTRO-APS) is ongoing but has undergone significant protocol amendments in light of safety concerns

regarding rivaroxaban in this group. A further study (RISAPS) will examine the potential role of higher intensity rivaroxaban in patients who have thrombotic antiphospholipid syndrome and cerebrovascular disease. Table 2 summarises the reported studies.

The RAPS study

The RAPS (Rivaroxaban vs warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus) study (Cohen et al, 2016) randomised 116 patients with thrombotic antiphospholipid syndrome of any laboratory profile to rivaroxaban 20 mg once a day or vitamin K antagonist (target international normalised ratio 2.5), excluding those with prior arterial events. The study used a laboratory primary end point of percentage change in endogenous thrombin potential from baseline to day 42. Endogenous thrombin potential is not based on coagulation times, but instead measures the total thrombin generation in an in-vitro system triggered by adding tissue factor. The occurrence of thromboembolism up to day 210 was included as a secondary end point.

The RAPS study authors reported rivaroxaban was inferior to vitamin K antagonist for the percentage change in endogenous thrombin potential, although with no thrombotic events in either group occurring in the relatively short period of follow up. The authors argued that the similar peak thrombin concentrations suggested non-inferiority of thrombotic risk.

The TRAPS study

The TRAPS (Trial on Rivaroxaban in Anti-Phospholipid Syndrome) study (Pengo et al, 2018) randomised high-risk triple positive antiphospholipid syndrome patients to rivaroxaban 20 mg once a day or vitamin K antagonist (target international normalised ratio 2.5) with a combined primary end point of venous and arterial thromboembolism, major bleeding and vascular death. The study used a non-inferiority design and planned to recruit 536 patients, but was terminated after the enrolment of just 120 because of an excess of arterial events and bleeding in the rivaroxaban group. In the per protocol analysis, there were 11 events (four ischaemic stroke, three myocardial infarction, four major bleeding) among 59 patients taking rivaroxaban and just two episodes of major bleeding in 61 patients taking vitamin K antagonist. The reasons for this excess are not clear. The TRAPS authors hypothesised that the effect may be related to reduced compliance in the direct oral anticoagulant group in the absence of therapeutic monitoring, a requirement for a higher effective dose of factor Xa inhibitor to prevent arterial as compared to venous thrombosis or the single factor inhibition of rivaroxaban as compared to the effect of vitamin K antagonists, which reduce levels of all the vitamin K-dependent factors.

The Rivaroxaban in Antiphospholipid Syndrome study

The Rivaroxaban in Antiphospholipid Syndrome study randomised 190 patients with thrombotic antiphospholipid syndrome with any laboratory profile to rivaroxaban 20 mg once a day or a vitamin K antagonist (target international normalised ratio 2.5 or 3.5 if recurrent thrombosis on anticoagulation) in a non-inferiority design (Ordi-Ros et al, 2019). The groups were well balanced for triple positive laboratory profile (roughly 60% of each group) and prior arterial events (roughly 35% of each group). Rivaroxaban failed to achieve non-inferiority in the primary composite end point of arterial or venous thrombosis and vascular death, and was associated with nearly double the rate of events (11 events in the rivaroxaban group as compared to six in the vitamin K antagonist group). Events in the rivaroxaban group were dominated by ischaemic stroke (nine events).

ASTRO-APS

The Astro-APS (Apixaban for the Secondary Prevention of Thrombosis Among Patients With Antiphospholipid Syndrome) study (Woller et al, 2018) is randomising antiphospholipid syndrome patients between twice daily factor Xa inhibitor apixaban or vitamin K antagonists (target international normalised ratio 2.5). This study is using a pragmatic definition of antiphospholipid syndrome, including those with a clinical diagnosis who report positive antiphospholipid antibody testing but without currently detectable antibodies. Following a pre-specified safety review the study has been amended to increase the dose of apixaban

Table 2. Reported randomised controlled trials evaluating direct oral anticoagulants in thrombotic antiphospholipid syndrome

Study and reference	Population	Primary endpoint	Design	Randomisation		Thrombotic events	Major bleeding events	Follow up	Result for primary outcome	Significance
RAPS (Cohen et al, 2016)	Thrombotic antiphospholipid syndrome on warfarin INR target 2.5	Change in endogenous thrombin potential	Non-inferiority	DOAC arm *n*=54	Rivaroxaban 20 mg once a day	0	0	All patients: 210 days	Endogenous thrombin potential higher in the rivaroxaban group: treatment effect 2·0, 95% CI 1·7–2·4	*P*<0.0001
				VKA arm *n*=56	Warfarin INR target 2.5	0	0			
TRAPS (Pengo et al, 2018)	Thrombotic antiphospholipid syndrome with triple positive laboratory profile	Cumulative incidence of thrombotic events, major bleeding, vascular death	Non-inferiority	DOAC arm *n*=59	Rivaroxaban 20 mg once a day	7 (12%)	4 (7%)	Mean: 569 days (18.7 months)	Study stopped because of excess events in rivaroxaban group: hazard ratio 6.7; 95% CI, 1.5–30.5.	*P*=0.008
				VKA arm *n*=61	Warfarin INR target 2.5	0	2 (3%)			
Rivaroxaban in APS study (Ordi-Ros et al, 2019)	Thrombotic antiphospholipid syndrome	Thrombotic events	Non-inferiority (margin 1.4)	DOAC arm *n*=95	Rivaroxaban 20 mg once a day	11 (11.6%)	6 (6.3%)	Mean 33.1 months	Rivaroxaban group 11.6%, VKA group 6.3% relative risk 1.83 CI 0.71 to 4.76	*P*=0.29 for non-inferiority
				VKA arm *n*=95	Warfarin INR target 2.5	6 (6.3%)	7 (7.4%)	Mean 34.1 months		

CI = confidence interval; DOAC = direct acting oral anticoagulant; INR= international normalised ratio; VKA = vitamin K antagonist

from 2.5 mg twice a day to the higher dose of 5 mg twice a day, and to exclude those with prior arterial events, including silent cerebral infarction on screening magnetic resonance imaging. The study will hopefully provide useful information for guiding decision making in patients with lower risk antiphospholipid syndrome and no prior arterial events who would prefer to avoid vitamin K antagonists.

Therefore, data from the two published randomised controlled trials with clinical primary end points support the concerns raised from observational data that direct oral anticoagulants appear to be inferior to vitamin K antagonists for the anticoagulation of higher risk patients with thrombotic antiphospholipid syndrome. Triple positive antibody status or prior arterial events are features which should raise particular concern.

Implications for UK practice

Direct oral anticoagulants are now frequently used instead of vitamin K antagonists as first-line anticoagulation for patients with venous thromboembolism in the UK because of their greater convenience, immediate efficacy, reassuring safety profile and much better cost efficacy (OpenPrescribing.net et al, 2020). Patients with clearly provoked venous thromboembolism (eg following hospital admission) have a low risk of recurrence and are typically anticoagulated for 3 months only. In those with an unprovoked venous thromboembolism or a venous thromboembolism following a weak provoking factor such as a long-haul flight, the decision about whether to continue anticoagulation is more nuanced. Antiphospholipid syndrome testing is one important consideration in a decision to discontinue anticoagulation, and full testing is typically deferred until beyond the initial 3-month treatment period when an interruption to anticoagulation for lupus anticoagulant detection can be considered more safely.

While the recently updated National Institute for Health and Care Excellence (2020) guidelines on *Venous thromboembolic disease: diagnosis, management and thrombophilia testing*, as well as European groups have recommended using vitamin K antagonists in preference to direct oral anticoagulants in those with triple positive antibody status only (Tektonidou et al, 2019), the European Medicines Agency and the UK Medicine and Healthcare products Regulatory Agency have gone further, suggesting that they should not be used in patients with antiphospholipid syndrome who have any positive tests for antiphospholipid syndrome. This includes a change of anticoagulant therapy to a vitamin K antagonist for triple positive patients with antiphospholipid syndrome who are already established on a direct oral anticoagulant. Given the limited data for lower risk patients, the British Society for Haematology guidance advises discussing their preferences with the patient before reaching a decision (Arachchillage et al, 2020).

These developments raise questions for UK practice and particularly the possibility that antiphospholipid syndrome testing should be carried out more extensively. The updated National Institute for Health and Care Excellence (2020) guidelines recommend considering testing patients for antiphospholipid antibodies who have unprovoked venous thromboembolism, and who might otherwise discontinue anticoagulation, acknowledging the need for specialist advice if patients are on anticoagulants at the time of testing. But these guidelines do not give guidance on testing patients who are continuing anticoagulation on a direct acting oral anticoagulant because of a lack of evidence. The updated British Society for Haematology guidance recommends testing selected patients with unprovoked venous thromboembolism who have clinical features identified in the Euro-Phospholipid registry (**Table 3**) at diagnosis for solid phase antiphospholipid antibodies (IgG/IgM anti-β2 glycoprotein-1 and anticardiolipin antibodies via ELISA). When positive, the test should be repeated after 12 weeks, along with lupus anticoagulant testing, if necessary under low molecular weight heparin cover. For patients in whom triple positive antiphospholipid syndrome is subsequently confirmed, long-term anticoagulation with a vitamin K antagonist is advised. The authors of the British Society for Haematology guidelines argue that testing unselected patients with unprovoked venous thromboembolism would be inefficient as only 10% will be positive (Andreoli et al, 2013), although there is a lack of data to indicate how sensitive a strategy guided by clinical features would be.

Table 3. Clinical features of patients who have had venous thromboembolism who have an increased likelihood of antiphospholipid syndrome
History of systemic lupus erythematosus or other autoimmune disease
Presence of livedo reticularis
Prolonged activated partial thromboplastin time before starting anticoagulation*
Recurrent thrombosis
Venous thromboembolism at unusual sites
History of arterial thrombosis without clear risk factors
Thrombocytopenia
Recurrent miscarriages, stillbirth or severe pre-eclampsia
Cardiac valve abnormalities in the absence of other explanations

*Adapted from Arachchillage et al (2020) with permission. * note reagents vary in sensitivity to lupus anticoagulants*

The implementation of initial testing and follow up will vary between institutions. The authors' practice is to test unselected patients with unprovoked venous thromboembolism in the context of a haematologist-led thrombosis clinic reviewing patients at 3 months, as illustrated in Figure 1, but approaches will vary between institutions depending on existing pathways for management of patients with venous thromboembolism.

While this approach resolves some management concerns, a number of issues remain unaddressed and in need of further investigation. First, whether patients who have an initial positive antiphospholipid test and who are treated with a direct oral anticoagulant pending confirmation are at significantly higher risk of recurrence. Second, limiting testing for lupus anticoagulant to those with a solid phase antiphospholipid antibody will miss some patients with antiphospholipid syndrome who remain on direct oral anticoagulants.

The authors' practice is to consider full antiphospholipid antibody testing for patients who have had a venous thromboembolism and are either planning to continue a direct oral anticoagulant long term or are considering switching from an established vitamin K antagonist to a direct oral anticoagulant, and for patients who have had an ischaemic stroke below the age of 50 years. The authors prefer vitamin K antagonists over direct oral anticoagulants for patients with triple positive antiphospholipid syndrome and any patient with current or previous arterial thrombotic events. There is uncertainty over the best approach for patients with venous thromboembolism who only have one or two positive tests for antiphospholipid syndrome and no history of arterial events, and the authors document an individualised discussion with each patient.

Future possibilities

Although clinical trial evidence suggests an increased thrombotic risk for patients with triple positive antiphospholipid syndrome on direct oral anticoagulants compared to vitamin K antagonists, the safety of direct oral anticoagulant use in patients with lower risk profiles remains uncertain. The ASTRO-APS study may provide further insights into this particular group.

The concern regarding the risks of arterial events for patients with antiphospholipid syndrome treated with direct oral anticoagulants may be further informed by the ongoing RIvaroxaban for Stroke Patients With AntiPhospholipid Syndrome (RISAPS) trial (NCT03684564). The investigators will compare changes in magnetic resonance imaging assessed white matter hyperdensity as an indicator of ischaemia as the primary outcome with patients randomised to higher intensity rivaroxaban 15 mg twice a day or vitamin K antagonist at an international normalised ratio target of 3.5.

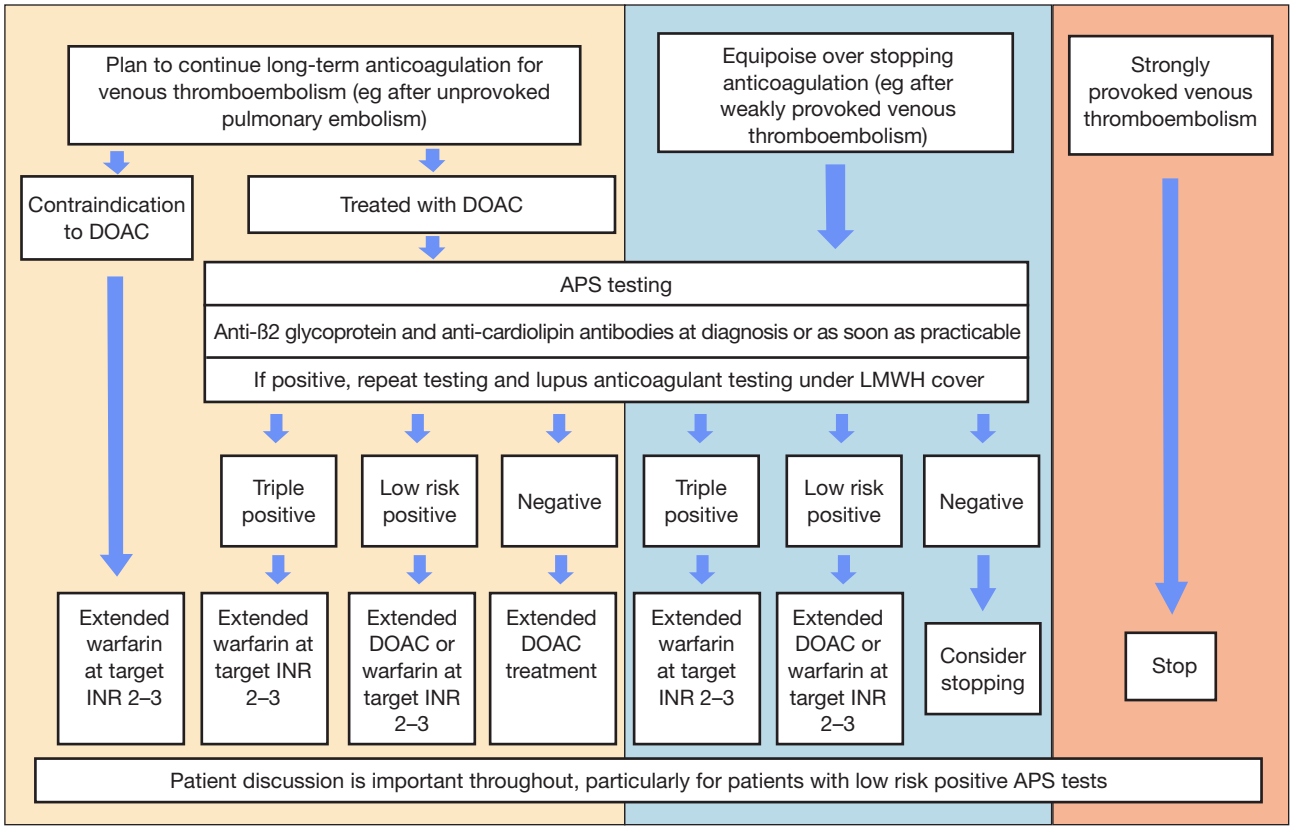

Figure 1. The role of antiphospholipid syndrome testing to guide extended anticoagulation beyond 3 months in patients with venous thromboembolism. APS = anti-phospholipid syndrome; DOAC = direct acting oral anticoagulant; INR = international normalised ratio; LMWH = low molecular weight heparin.

Conclusions

Although direct oral anticoagulants have offered considerable advantages to vitamin K antagonists for many patients with venous thromboembolism, recent evidence has demonstrated safety concerns for patients with antiphospholipid syndrome, particularly those with the highest risk laboratory profiles or a history of arterial events. Consequently, consideration should be given to using vitamin K antagonists in preference to a direct oral anticoagulant in these populations.

Author contribution

Stephen Booth and Kieran Burton contributed equally to this article.

Key points

- Testing for lupus anticoagulant while on direct oral anticoagulants is unreliable unless specialised tests are used; discuss testing with your local laboratory.
- Testing for anti-cardiolipin antibodies and anti-ß2 glycoprotein 1 antibodies by enzyme-linked immunosorbent assay is unaffected by direct oral anticoagulants.
- Randomised controlled trial evidence demonstrates significantly higher rates of recurrent thrombosis, particularly arterial events, with rivaroxaban compared to warfarin in the treatment of high-risk antiphospholipid syndrome.
- Medicines and Healthcare products Regulatory Agency guidance advises against use of direct oral anticoagulants in patients with antiphospholipid syndrome.
- Antiphospholipid syndrome testing is likely to become relevant to many more patients with unprovoked venous thromboembolism, particularly those with clinical features raising suspicion of antiphospholipid syndrome.

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Conflicts of interest

The authors declare no conflicts of interest..

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